



Bioequivalence of oxcarbazepine oral suspension vs. film-coated tablet in healthy Chinese male subjects

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Key words

oxcarbazepine – trileptal – monohydroxy derivative (MHD) – bioequivalence – Chinese male subjects

Abstract. Objective: Oxcarbazepine (Trileptal®) is an antiepileptic drug used as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children. The primary objective of this study was to assess the bioequivalence of Trileptal® oral suspension formulation vs. the film-coated tablet after single and multiple twice-daily administrations in fasted, healthy Chinese male subjects. Methods: This was an open-label, randomized, two-period crossover study in 19 healthy Chinese male subjects. Treatment periods consisted of a single dose of 300 mg oxcarbazepine (either oral suspension formulation or film-coated tablet) on Day 1, b.i.d. administrations of 300 mg from Day 4 to Day 8 inclusive, and a final dose of 300 mg on the morning of Day 9. A 1-week washout period was implemented between treatment periods. Plasma levels of 10-monohydroxy derivative (MHD), the main metabolite mediating the pharmacologic activity of oxcarbazepine, were measured by a validated liquid chromatography tandem mass spectrometry method. Bioequivalence was assessed by the MHD areas under the concentration time curve (AUCs) and maximum concentrations (C_{max}) of the oral suspension vs. the film-coated tablet. Safety was evaluated throughout the study. Results: Trileptal® oral suspension formulation was bioequivalent to film-coated tablet after single dose and multiple b.i.d. administrations, as assessed by MHD AUCs and C_{max} . The 90% confidence intervals (CI) of the geometric mean of the MHD individual ratios were within the bioequivalence CI limits (0.80-1.25). No safety concerns were raised. Conclusions: Trileptal® oral suspension formulation and film-coated tablets are bioequivalent in healthy Chinese males.

antiepileptic drug registered worldwide by Novartis (Basel, Switzerland) under the trade name Trileptal®. The pharmacologic activity of oxcarbazepine is primarily mediated by its metabolite, 10-monohydroxy derivative (MHD; 10,11-dihydro-10-hydroxy-carbamazepine) [Flesch 2004], which is obtained by the reduction of oxcarbazepine by cytosolic enzymes [Schuetz et al. 1986]. When 400 mg ¹⁴C-oxcarbazepine was given to 2 healthy subjects, 68% of the total radioactivity in plasma was due to MHD and 6% was due to the pharmacologically inactive dihydroxy derivative, whereas unchanged oxcarbazepine contributed to only 2%, and the remainder was attributable to minor secondary metabolites [Feldman et al. 1981]. In addition, plasma concentrations of MHD persisted longer than those of unchanged oxcarbazepine after a single oral administration.

In the European Union and the United States, oxcarbazepine film-coated tablets and oral suspension formulations are approved for use as monotherapy or adjunctive therapy for the treatment of partial seizures in adults and children. Oxcarbazepine is approved for use as adjunctive therapy or monotherapy in children aged ≥ 6 years in the European Union, and as monotherapy in children aged ≥ 4 years and adjunctive therapy in children aged ≥ 2 years in the United States. Oxcarbazepine is also approved for the treatment of generalized tonic-clonic seizures in adults and children in South America, Australia, and other countries. The age range for treatment in children varies in those countries.

Trileptal® film-coated tablets (150 mg and 300 mg) were approved in China in 2003 for the treatment of partial seizures in adults and children; however, the oral suspension

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Introduction

Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide) is an

formulation has not yet been approved. In this country, oxcarbazepine is indicated for use as monotherapy and as adjunctive therapy for the treatment of partial seizures (with or without secondary generalized tonic-clonic seizures) in adults and in children over 5 years of age. This study was designed to assess the bioequivalence of Trileptal® oral suspension manufactured by Novartis Pharma SAS vs. Trileptal® film-coated tablet available in China, in Chinese healthy male subjects, in order to gain regulatory approval of Trileptal® oral suspension for clinical use in China.

Materials and methods

Subjects

Chinese male subjects aged 18–45 years inclusive, in good health as assessed by their past medical history, physical examination, vital signs, electrocardiogram (ECG) and laboratory tests, were eligible for inclusion. Oral body temperature had to be between 35 and 37.5 °C; systolic blood pressure between 90 and 140 mmHg; diastolic blood pressure between 40 and 100 mmHg; and pulse rate between 40 and 90 beats per minute. In addition, subjects had to have a body mass index between 19 and 24 and weigh at least 50 kg. Subjects had to consent to using double-barrier contraception (condom plus spermicidal gel) and refrain from fathering a child in the 3 months following the last drug administration in the study. Subjects were excluded if they: were smokers (in the previous 3 months or during the study); had taken prescription drugs (with the exception of paracetamol), vitamins, herbal supplements, or dietary supplements within 4 weeks of the first dose of the study drug; participated in any clinical investigation within 4 weeks of the first dose of the study drug; donated or lost ≥ 400 ml blood within 8 weeks of the first dose of the study drug; had a significant illness within 2 weeks of the first dose of the study drug; had a history or family history of ECG abnormalities; had a history of autonomic dysfunction (e.g. orthostatic hypotension); had acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease) or drug/atopic allergies. Subjects were also excluded if they had any surgical or medical

condition that may alter drug pharmacokinetics. A positive HIV or hepatitis C test also excluded the subject from the study. Subjects were ineligible if they demonstrated a history of drug or alcohol abuse, as indicated by laboratory tests.

The power calculation was originally based on the estimates of the intra-subject coefficient of variation for AUC and C_{\max} (for single dose and steady state) of 0.06–0.12 observed in a previous study in healthy, non-Chinese males [Flesch et al. 2003]. Based on the current knowledge of oxcarbazepine metabolism, the pharmacokinetics of oxcarbazepine was not expected to vary with race. To ensure 90% power of the statistical analysis, 10 subjects were required to complete the study. However, this number was less than the Chinese State Food and Drug Administration Bioequivalence and Bioavailability Study Guidance for Chemical Drugs recommendation [State Food and Drug Administration 2004], i.e. 18 subjects. Therefore, 20 healthy Chinese male subjects were enrolled to ensure a minimum of 18 subjects completed the study.

Study design and population

The study was an open-label, randomized, two-period crossover design in healthy Chinese male subjects. The subjects were randomly assigned (block-wise randomization) to treatment groups using a validated system that generates an automated random assignment of randomization numbers to treatment groups. The primary objective was to assess the bioequivalence of Trileptal® 60 mg/ml oral suspension (manufactured by Novartis Pharma SAS) vs. 300 mg film-coated tablet (manufactured by Novartis Schweiz AG, purchased from a Chinese wholesaler) after multiple b.i.d. administrations of 300 mg oxcarbazepine (5 ml of the oral suspension). The bioequivalence of the two formulations after a single 300 mg administration was studied as a secondary objective.

The study consisted of a 21-day screening period and two treatment periods (suspension or tablet), each preceded by a 1-day baseline period and a study evaluation 12 h after the last drug administration. During one treatment period, subjects received a single ad-

ministration of 300 mg oxcarbazepine oral suspension formulation on Day 1; b.i.d. doses of 300 mg oxcarbazepine oral suspension formulation at 12-h intervals on Days 4 – 8; and 300 mg oxcarbazepine oral suspension formulation on Day 9. The other treatment period comprised of a single dose of 300 mg oxcarbazepine film-coated tablet on Day 1; b.i.d. doses of 300 mg film-coated tablet on Days 4 – 8; and a single dose of 300 mg oxcarbazepine film-coated tablet on Day 9. A wash-out period of 7 days was implemented between the two treatment periods to avoid any carry-over from the first period to the second. The study medication was administered between 7.30 and 9.00 am on Days 1 and 9. On Days 4 – 8, the study drug was administered within 1 h of breakfast or the evening meal, 12 h apart. Each administration was taken with 240 ml of water under fasting conditions. Alcoholic beverages were not permitted 72 h before the first dose of the study drug until the evaluation at the end of the study. Xanthine-containing food or beverages were discontinued 48 h before the first dose of the study drug until the end of the study.

For assessment of plasma drug concentrations, 1 ml blood samples were taken by direct venopuncture or an indwelling catheter inserted into a forearm vein at the following times: Day 1: pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 32, 48, 56 and 72 h after the morning administration of oxcarbazepine; Day 8: before the morning and evening administrations of oxcarbazepine; Day 9: pre-dose and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h after the morning administration of oxcarbazepine. Blood samples were collected in heparinized tubes and centrifuged at 3 – 5 °C for 15 min at 1,500 × g. Plasma was transferred to polypropylene screw-cap tubes and frozen within 30 min of venopuncture at or below –18 °C until analysis.

The study was performed in the Clinical Pharmacology Research Center, Peking Union Medical College Hospital, Beijing, China. It was approved by the Ethics Committee of Peking Union Medical College Hospital and was conducted according to the ethical principles of the Declaration of Helsinki, Venice, Hong Kong and Somerset West amendments 1983, 1989 and 1996 [The World Medical Association 2007], in compliance with Good Clinical Practice [ICH har-

monized tripartite guideline: Guideline for Good Clinical Practice 2001].

Drug analysis

MHD plasma concentrations were determined using a validated high-throughput, specific and sensitive liquid chromatography tandem mass spectrometry (MS/MS) method. MHD and its labeled internal standard were extracted using a solid-phase extraction with manually processed 3M Empore® C₁₈ 96-well plates. After conditioning of the sorbent with methanol and water, plasma samples diluted with the internal standard were loaded on the plates and wells were washed with water followed by water-methanol (80:20 v/v). Analytes were eluted with methanol and diluted in water. Extracts were injected onto a Zorbax stable-bond C₁₈ column (3.5 µm, 30 × 4.6 mm, Agilent, Santa Clara, CA, USA) using 20 mM ammonium acetate-(methanol-acetonitrile 55:45, v/v) 45:55 v/v at 0.5 ml/min as a mobile phase and analyzed by MS/MS (API4000, Applied Biosystems, Foster City, CA, USA) in multiple-reaction monitoring mode using atmospheric pressure chemical ionization as an interface. The MHD standard curves were analyzed daily and ranged from 0.1 to 200 µmol/l. The lower limit of quantification (LLOQ) was 0.1 µmol/l using 75 µl of plasma. The analysis was validated using quality-control samples in addition to the study samples. Overall precision, as assessed by percent coefficient of variation of replicate analysis, was 3.8, 3.5 and 3.2% for low (0.296 µmol/l), medium (17.4 µmol/l), and high (174 µmol/l) quality control samples, respectively, and the mean accuracies were 2.5, 4, and –0.5%, respectively.

Pharmacokinetic evaluation

All subjects who completed the study were included in the pharmacokinetic data analysis. Pharmacokinetic parameters were determined on Days 1 and 9 from plasma concentrations of MHD by non-compartmental methods using WinNonlin® Professional version 5.0.1. Only MHD was measured in plasma samples as oxcarbazepine is a pro-drug

(see introduction section) and this main metabolite accounts for the most of the pharmacologic activity [Flesch 2004].

Steady state

The primary MHD pharmacokinetic parameters calculated during steady state were the maximum steady state concentration during the dosing interval (C_{\max}^{ss}) and area under the concentration-time curve (AUC) over the dosing interval (τ) at steady state (AUC_{τ}). These primary pharmacokinetic parameters were used to assess bioequivalence after multiple b.i.d. oral suspension and film-coated tablet administrations. Secondary MHD pharmacokinetic parameters included the minimum concentration during the dosing interval (C_{\min}^{ss}), average steady-state concentration during the dosing interval (C_{av}^{ss} , determined as AUC_{τ}/τ) and fluctuation index (calculated as $[(C_{\max}^{ss} - C_{\min}^{ss})/C_{av}^{ss}] \times 100$). The ratio of AUC_{τ} at steady state over $AUC_{0-\infty}$ after a single dose to explore time-dependent pharmacokinetics was also calculated.

Single dose

The primary MHD pharmacokinetic parameters calculated following single doses of oxcarbazepine were C_{\max} , AUC_{0-t} and $AUC_{0-\infty}$ (calculated using the linear trapezoidal method: $AUC_{\text{last}} + C_t/k$, where AUC_{last}

is the AUC from 0 to the last sample where concentration was above the LLOQ, C_t is the concentration at time t and k is the terminal elimination-rate constant). These primary pharmacokinetic parameters were used to assess bioequivalence after single doses of oral suspension and film-coated tablet. Secondary MHD pharmacokinetic parameters calculated included t_{\max} , determined as the time at which C_{\max} occurs, and the terminal half-life ($t_{1/2}$).

Safety evaluation

Safety was assessed through hematology, blood chemistry, urine, vital signs, physical condition and body weight assessments. No formal analyses of safety data were carried out. All adverse events were recorded.

Statistical evaluation

AUC_{τ} and C_{\max}^{ss} after repeated doses and $AUC_{0-\infty}$, AUC_{last} and C_{\max} after a single dose were log-transformed (base e) prior to separate analysis using a mixed model as follows: response = sequence + subject (sequence) + treatment + period + random error. The point estimate and 90% confidence interval (CI) for the difference between the treatments on the log scale were back-transformed and calculated from this model.

Bioequivalence was considered separately for multiple and single dosing by assessment of the primary pharmacokinetic parameters, and was accepted if the 90% CIs for the ratios of the populations were between the no-effect values (0.80, 1.25). No formal statistical evaluations were made for the secondary pharmacokinetic parameters or safety.

Results

Subjects

In total, 84 subjects were screened and 20 were eligible for the study. One subject did not receive the study drug due to tachycardia on the morning of Day 1 before dosing (pulse rate was above 90 bpm). Therefore, 19 subjects were randomized and included in the

Table 1. MHD multiple-dose pharmacokinetics after b.i.d. oral administrations of 300 mg Trileptal® as an oral suspension and a film-coated tablet in 19 healthy male Chinese subjects.

	Oral suspension	Film-coated tablet
Primary pharmacokinetic parameters		
C_{\max}^{ss} ($\mu\text{mol/l}$)	45.0 (30)	47.3 (14)
AUC_{τ} ($\text{h} \times \mu\text{mol/l}$)	442 (37)	468 (15)
Secondary pharmacokinetic parameters		
t_{\max}^{ss} (hours) median (range)	3.0 (1.0 – 8.0)	4.0 (2.0 – 6.0)
C_{\min}^{ss} ($\mu\text{mol/l}$)	28.9 (49)	30.9 (18)
C_{av}^{ss} ($\mu\text{mol/l}$)	36.9 (37)	39.4 (15)
FI (%)	41.3 (31)	40.3 (34)
$AUC_{\tau-\text{Day 9}}/AUC_{\infty-\text{Day 1}}$	1.5 (15)	1.5 (10)

Values are geometric mean (% geometric mean coefficient of variation) not adjusted for sequence and treatment.

Table 2. Statistical analysis of the primary MHD pharmacokinetic parameters after multiple b.i.d. oral administrations of 300 mg Trileptal® as an oral suspension vs. a film-coated tablet in 19 healthy male Chinese subjects.

	Adjusted geometric mean ^a		Geometric mean ratio ^a		
	Oral suspension	Film-coated tablet	Estimate	Lower 90% CI	Upper 90% CI
C_{\max}^{ss} (μmol/l)	45.2	47.3	0.96	0.86	1.06
AUC_{τ} (h × μmol/l)	444.4	468.2	0.95	0.85	1.06

^a adjusted for sequence and treatment.

Table 3. MHD single-dose pharmacokinetics after oral administration of 300 mg Trileptal® as an oral suspension and a film-coated tablet in 19 healthy male Chinese subjects.

	Oral suspension	Film-coated tablet
Primary pharmacokinetic parameters		
C_{\max} (μmol/l)	17.5 (16)	18.2 (22)
$AUC_{0-\infty}$ (h × μmol/l)	298 (26)	317 (15)
Secondary pharmacokinetic parameters		
t_{\max} (hours) median (range)	3.0 (2.0 – 8.0)	4.0 (3.0 – 6.0)
AUC_{last} (h × μmol/l)	295 (26)	314 (15)
$t_{1/2}$ (hours) (lower and upper limits for estimation)	7.4 (21) (24 – 72)	7.6 (17) (24 – 72)

Values are geometric mean (% geometric mean coefficient of variation) not adjusted for sequence and treatment.

Table 4. Statistical analysis of the primary MHD pharmacokinetic parameters after a single oral administration of 300 mg Trileptal® as an oral suspension vs. film-coated tablet in 19 healthy male Chinese subjects.

	Adjusted geometric mean ^a		Geometric mean ratio ^a		
	Oral suspension	Film-coated tablet	Estimate	Lower 90% CI	Upper 90% CI
C_{\max} (μmol/l)	17.4	18.1	0.96	0.90	1.02
AUC_{0-t} (h × μmol/l)	296.3	314.3	0.94	0.88	1.01
$AUC_{0-\infty}$ (h × μmol/l)	298.8	316.7	0.94	0.88	1.01

^a adjusted for sequence and treatment.

Pharmacokinetics

The primary and secondary pharmacokinetic parameters of MHD after 5.5 days of multiple b.i.d. oral suspension and film-coated tablet administrations of 300 mg Trileptal® are shown in Table 1. The observed 90% CI of the geometric mean of the individual ratios for the primary MHD pharmacokinetic parameters, C_{\max}^{ss} and AUC_{τ} were within the CI for testing bioequivalence (0.80, 1.25) as shown in Table 2. These data demonstrate that the two Trileptal® formulations are bioequivalent after multiple b.i.d. administrations.

The primary and secondary pharmacokinetic parameters of MHD after a single administration of the oral suspension formulation and the film-coated tablet are shown in Table 3. The observed 90% CI interval of the geometric mean of the individual ratios for the primary MHD pharmacokinetic parameters, C_{\max} , AUC_{last} , and $AUC_{0-\infty}$ were within the CI for testing bioequivalence (0.80, 1.25) as shown in Table 4. These data demonstrate that the two Trileptal® formulations are bioequivalent after single dose administration.

Figures 1 and 2 show the similarity in the mean plasma concentration-time profiles between both formulations of MHD after repeated and single doses of oxcarbazepine, respectively. The MHD multiple-dose and single-dose pharmacokinetic parameters of the oral suspension formulation and film-coated tablets demonstrated similar pharmacokinetics, as shown in Tables 1 and 3, respectively, with the exception of t_{\max} which was 1 hour shorter after administration of the oral suspension formulation compared with the film-coated tablet.

After single and multiple b.i.d. administrations of the oral suspension, 1 subject showed unexpected low bioavailability compared with other subjects. This subject's individual C_{\max}^{ss} and AUC_{τ} were 30% and 23% of those of the other 18 subjects, respectively. However, this subject did not show such a low bioavailability after multiple b.i.d. doses of the film-coated tablet. Consequently, as a result of this outlier, inter-subject variability in MHD C_{\max}^{ss} , AUC_{τ} , C_{\min}^{ss} and C_{av}^{ss} was more than 2-fold higher after the oral suspension formulation compared with the film-coated tablet.

pharmacokinetic analysis; 9 in the suspension/tablet sequence group (Group 1) and 10 in the tablet/suspension sequence group (Group 2). The age range in each group was 19 – 35 years. The weight range was 59 – 69 kg in Group 1 and 51 – 74 kg in Group 2.

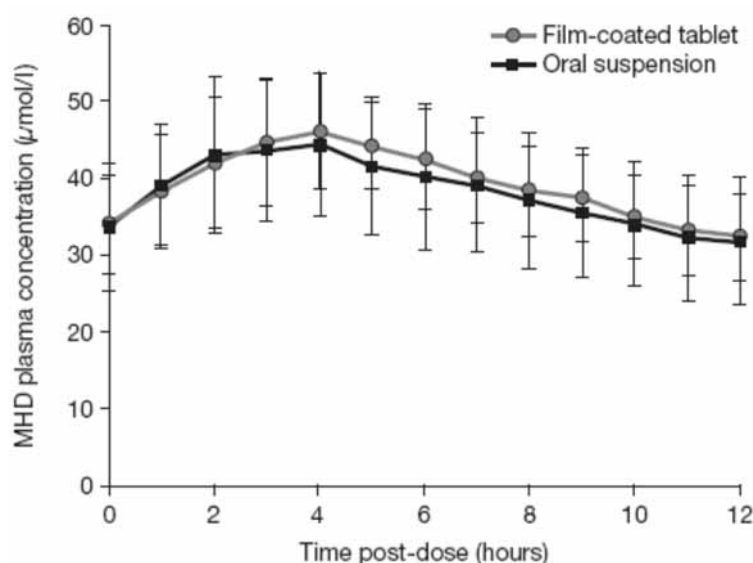


Figure 1. Arithmetic mean (SD) MHD plasma concentration-time profiles after repeated b.i.d. doses of 300 mg Trileptal® as an oral suspension and a film-coated tablet in 19 healthy male Chinese subjects.

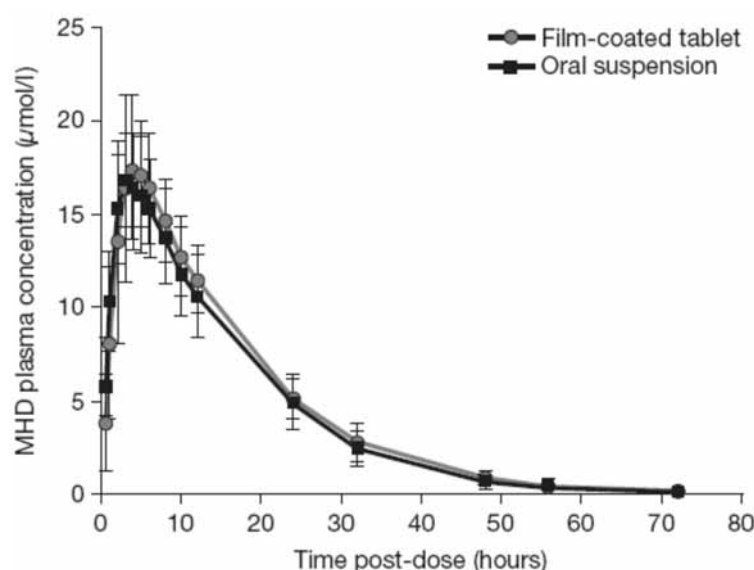


Figure 2. Arithmetic mean (SD) MHD plasma concentrations after a single dose of 300 mg Trileptal® as an oral suspension and a film-coated tablet in 19 healthy male Chinese subjects.

(up to 80 U/l) and γ -glutamyltransferase (up to 103 U/l)), not associated with clinical symptoms, were reported as drug-related adverse events. Three of these occurred during administration of the oral suspension formulation and two occurred during treatment with the film-coated tablet. All liver enzymes returned to normal ranges when tested post-study. One skull injury (skin laceration) was not deemed to be related to the study drug. No other safety concerns were reported.

Discussion

This is the first study to assess the bioequivalence of oral suspension and film-coated tablet formulations of Trileptal® in healthy Chinese subjects. Trileptal® oral suspension formulation was bioequivalent to the film-coated tablet after 300 mg multiple b.i.d. administrations with respect to the primary MHD pharmacokinetic parameters, AUC_{τ} and C_{max}^{ss} . In addition, the formulations were bioequivalent after a single 300 mg administration with respect to the primary MHD pharmacokinetic parameters, $AUC_{0-\infty}$, AUC_{last} , and C_{max} . Moreover, the similarity of the oxcarbazepine pharmacokinetics from the two formulations was supported by the secondary pharmacokinetic parameters. In particular, C_{min}^{ss} , C_{av}^{ss} , FI, and $t_{1/2}$ after a single dose were similar for the two formulations. The ratio of AUC_{τ} at steady state over $AUC_{0-\infty}$ after a single dose was 1.5 for the two formulations suggesting similar non-clinically relevant time dependency in oxcarbazepine pharmacokinetics due to a slight accumulation of MHD over time. t_{max} was shortened by approximately 1 hour after administration of the oral suspension formulation compared with the film-coated tablet after both single and multiple b.i.d. administrations, consistent with a faster systemic bioavailability of an oral suspension formulation compared with a tablet.

One subject showed unexpected low bioavailability of MHD after single and multiple b.i.d. doses of the Trileptal® oral suspension formulation, but did not show such unexpected pharmacokinetics after multiple b.i.d. doses of the film-coated tablet. No vomiting or dose volume error was recorded for this subject, which may have provided an expla-

Safety

The incidence of adverse events was similar in the two treatment sequence groups, with 3 subjects reporting events for each treatment. Five cases of one or more mild liver enzyme elevations (alanine aminotransferase (up to 144 U/l), aspartate aminotransferase

nation for this result. A lower bioavailability for an oral suspension formulation compared with a film-coated tablet is unlikely to occur; therefore, it may be possible that an error was not reported. This subject increased the inter-subject variability in the oral suspension group approximately 2-fold but the inter-subject variability of the two formulations was similar and low when this outlier was excluded from the analysis (data not shown). More relevantly, the two Trileptal® formulations were bioequivalent after single and multiple b.i.d. administrations with the outlier included in the statistical analysis.

A similar oxcarbazepine pharmacokinetics study has been performed in healthy Caucasian subjects, which assessed the bioequivalence of two Trileptal® oral suspension formulations vs. the film-coated tablet formulation [Flesch et al. 2003]. Results of the present study in Chinese subjects (receiving 300 mg oxcarbazepine) are similar to those in Caucasians (receiving 600 mg oxcarbazepine). However, in the Caucasian study, the MHD C_{max} was slightly outside the upper limit of bioequivalence CI boundary of 0.80, 1.25 for comparison of the two formulations after a single dose of oxcarbazepine. These single-dose findings are not of clinical importance as oxcarbazepine is intended to be administered as a chronic maintenance treatment (titrated for efficacy), with plasma concentrations of MHD being maintained at steady state. In addition, the dose-normalized MHD pharmacokinetic parameters observed in the present study were close to those reported in the Caucasian study [Flesch et al. 2003] suggesting that oxcarbazepine pharmacokinetics are insensitive to ethnic factors.

In summary, the MHD pharmacokinetics observed in the present study of Chinese subjects demonstrate that the film-coated tablet and oral suspension formulation of oxcarbazepine are bioequivalent after multiple and single administrations of 300 mg. These findings are consistent with those from Caucasian subjects. Therefore oxcarbazepine pharmacokinetics are considered to be insensitive to intrinsic ethnic factors of the Chinese population. Trileptal® 300 mg administered as 60 mg/ml oral suspension and 300 mg film-coated tablet twice daily for 5.5 days were well tolerated in healthy male Chinese subjects.

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